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10/059,521	01/29/2002	Ivan N. Rich	R103 1030.1	5794

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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/059,521	RICH, IVAN N.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28,31,42-44,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28,31,42-44,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and arguments, filed on May 12, 2006, is acknowledged and has been entered. Claim 1 has been amended. Currently, claims 1-28, 31, 42-44, 57, and 58 are pending and are under examination.

Withdrawn Rejections

2. All rejections not reiterated herein, have been withdrawn.

3. In light of Applicant's amendment and arguments, the rejection of claims 1-28, 31, 42-44, 57, and 58 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn

4. In light of Applicant's amendment and arguments, the rejection of claims 1-28, 31, 42-44, 57, and 58 under 35 U.S.C. 112, first paragraph, is hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-28, 31, 42-44, 57, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouch et al. (Journal of Immunological Methods, 160: 81-88 (1993))

in view of Bell et al. (US 2002/0120098 A1) and in further view of Moore et al. (US Patent 5,328,844) for reasons of record.

Crouch et al. disclose an assay method for determining the proliferative status, i.e. cell proliferation, of a population of primitive hematopoietic cells. The hematopoietic cells are granulocyte-macrophage colony-forming cells (GM-CFC) and granulocyte colony-forming cells (G-CFC), i.e. TF-1 and NFS-60 cells, isolated from human peripheral blood, and are detected for cytokine dependent proliferation by stimulation of granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) (see Abstract). Initially, the hematopoietic cell lines from peripheral blood are cultured and maintained in a cell growth culture medium containing 0% to 30% (12.5%) fetal bovine serum (fetal calf serum). Crouch et al. then isolate mononuclear cells (MNCs) from peripheral blood, i.e. containing hemoglobin, in order to render the MNC sample substantially free of hemoglobin. Crouch et al. isolate the MNCs by Ficoll-Hypaque density gradient centrifugation. For ATP bioluminescence assay, Crouch et al. specifically contacts the isolated MNCs with luciferin-luciferase monitoring reagent which generates bioluminescence in the presence of adenosine triphosphate or ATP (see page 81, column 2 and page 82, columns 1 and 2). The amount of luminescence generated by the reagent indicates the amount of ATP in the MNC cell population, wherein the amount of ATP indicates the proliferative status of the hematopoietic cells.

Crouch et al. differ from the instant invention in failing to disclose that the cell growth culture medium includes methylcellulose having a concentration of about 0.4%

to 0.7%, transferrin with at least one cytokine, and maintained in an atmosphere having between about 3.5% to 7.5% oxygen. Crouch et al. also does not teach generating a hematopoietic population enriched in progenitor cells and stem cells from animal tissue such as bone marrow, fetal liver, and spleen, isolated from cow, sheep, pig, horse, goat, dog, cat, and primates, and determining their suitability for transplantation, and isolating and identifying specific subpopulations of primitive hematopoietic cells using cell surface markers. Lastly, Crouch et al. does not teach contacting the hematopoietic cells with a test compound and determining its ability to modulate proliferation of the cells.

Bell et al. disclose compositions and methods comprising heme-containing components for use in inducing and/or enhancing stimulation of erythropoiesis, a subclass of hematopoiesis, in order to hence, stimulate erythroid progenitor proliferation in a cell culture system. Hematopoiesis involves the proliferation of hematopoietic stem cells and hematopoietic progenitor cells and the stimulation is specific for hematopoietic colony-forming cell erythroid macrophage, megakaryocyte stem cells (CFC-GEMM) (see page 4, column 1, [0026], page 7, column 2, [0071], and page 9, column 2, [0085]). According to Bell et al., the burst forming unit-erythroid (BFU-E) represents the most primitive hematopoietic or erythroid progenitor and forms large multi-clustered hemoglobinized colonies (see page 1, column 1, [0004]). In practice, Bell et al. teach culturing the primitive hematopoietic cells in a cell growth medium comprising 30% fetal bovine serum, about 0.4% to about 0.7% (0.8%) methyl cellulose which increases viscosity in culture media, and in an atmosphere having between about 3.5% to 7.5% (5%) oxygen. Bell et al. also teach contacting the sample with cytokine such as GM-

CSF and Flt3 Ligand to generate a cell population substantially enriched in CFC-GEMM stem cells for use in cell proliferation assay (see page 7, column 2, [0071], page 9, column 2, [0084-0092], and Examples 1 and 2). According to Bell et al., erythroid progenitor colony formation is enhanced at lower, more physiological oxygen tensions, such as 5% oxygen (see page 11, column 1, [0098-0101]. These enriched hematopoietic stem cells or progenitor cells are obtained from bone marrow, cord blood, or peripheral blood, and if determined to have adequate proliferative status, can be transplanted into a recipient patient (see page 4, column 2, [0030] and page 7, column 2, [0078]). Hematopoietic stem cells or progenitor cells can also be obtained and enriched from animal tissue such as bone marrow, cord blood, fetal liver, or spleen, of dog, cow, horse, cat, pig, sheep, goat, chicken, primate, or human (see page 8, column 2, [0076-0078]). Subpopulations of primitive hematopoietic cells are characterized by the presence of specific hematopoietic progenitor cell surface markers such as CD34 and glycophorin A (see page 12, column 1, [0105]). These cell subpopulations can be selectively isolated and purified from other cells (cord blood) and other [heme-containing] sample components by binding the cells with antibodies specific for their cell surface markers such as anti-CD34 and anti-glycophorin A or by magnetic bead separation, i.e. STEMSEP™ system, and other separation systems, i.e. CEPRATE LC system, and selectively determining their identity by flow cytometry or flow activated cell sorting (see page 17, column 1, [0144 and 0145] and Example 9). Bell et al. further teach contacting primitive hematopoietic cells having a target cell population with a test a compound (Ganciclovir) and determining its ability to modulate, i.e. inhibit,

proliferation or differentiation of the target cell population. Result of the testing is compared with negative control (see Example 11).

Moore et al. disclose the beneficial effect of iron-saturated transferrin in mammalian cell growth media. Moore et al. specifically taught that when iron-saturated transferrin is added, other iron salts are not required. According to Moore et al., the function of transferrin in culture growth media is to act as an iron transport protein for the cells. See column 13, lines 52-65 and column 14, lines 30-44.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the culture growth media composition as taught by Bell having 30% fetal bovine serum, 0.8% methyl cellulose, and in an atmosphere having between about 5% oxygen, and to include therein transferrin taught by Moore, for the culture system as taught by Crouch for maintaining cells suitable for ATP bioluminescence assay, because Bell specifically taught that hematopoietic progenitor cells or stem cells favor survival and growth in a medium having such composition for use in any proliferation assays. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the culture system as taught by Bell and complimented with transferrin by Moore, which stimulates proliferation of hematopoietic cells culture growth media, for subsequent use as MNC sample for testing proliferation status using the ATP bioluminescence assay as taught by Crouch, because Bell specifically taught that erythroid progenitor colony formation is even further enhanced at lower, more physiological oxygen tensions, i.e. 5% oxygen; hence, increasing the concentration of hematopoietic progenitor cells for use in assays that

measure proliferation of cell populations, including the ATP bioluminescence assay taught by Crouch.

Response to Arguments

6. Applicant's arguments filed on May 12, 2006 have been fully considered but they are not persuasive.

A) Applicant argues that Bell involves preparation and use of growth media designed to stimulate hematopoietic progenitor growth cells, specifically erythroid progenitors. Applicant specifically contends that hematopoiesis and erythropoiesis do not describe the same thing because hematopoiesis refers to formation of blood cellular components and erythropoiesis refers to formation of erythrocytes; hence, Bell is only concerned with cells involved in erythropoiesis, i.e. erythrocytes and erythroblasts.

In response, erythroid progenitor cells which form into erythroblasts and erythrocytes are a subclass of hematopoietic cells. Accordingly, claim 1 does not exclude the primitive erythropoietic cells incubated in culture media as taught in the method of Bell. Additionally, as Bell teaches that fetal bovine serum (FBS), methylcellulose, and oxygen atmosphere within the parameters recited in the claims, cause erythropoietic cell growth, then it is maintained that Bell suggests the claimed invention.

B) Applicant argues that it would not have been obvious to one skilled in the art at the time of the instant invention to add transferrin discussed in Moore into a

hematopoietic culture medium because Moore is concerned with culture media that are formulated and optimized for the establishment and maintenance of effective mammalian cell growth for general or specialized purposes such as transporting iron to cells; but nowhere in Moore is it specifically taught to use transferrin to stimulate hematopoiesis. Applicant contends that Moore only addresses hematopoiesis with respect to other media supplements such as 2-mercaptoethanol; however, Moore would not have known whether transferrin has a beneficial effect on all cells of the hematopoietic system.

In response, the instant claims and disclosure do not recite or disclose functional use of transferrin to stimulate hematopoiesis; but rather recites use of transferrin as part of a culture system that stimulates hematopoiesis. Additionally, Applicant has not provided in the disclosure or in his response, what special beneficial effect transferrin has to contribute individually towards the claimed culture system for hematopoietic cells, that is distinct from its function that is taught in prior art (Moore). Accordingly, the teaching of Moore of transferrin appears to be consonant with that taught in the claimed invention. Absent evidence to the contrary, transferrin as used in the claimed invention is deemed to be for the general purpose of transporting iron into cells.

C) Applicant argues that Bell, Moore, or Crouch do not disclose the addition of growth media of at least one cytokine, as recited in the amended claims.

Contrary to Applicant's argument, Bell teaches adding at least one cytokine to the growth media for contact with the sample. The cytokine may be any one of GM-

CSF and Flt3 Ligand to generate a cell population substantially enriched in CFC-GEMM stem cells for use in cell proliferation assay (see page 7, column 2, [0071], page 9, column 2, [0084-0092], and Examples 1 and 2). Accordingly, it is maintained that the combined teaching of Bell, Moore, and Crouch suggests the claimed invention.

Response to Applicant's Declaration under 37 CFR 1.132

7. A) Dr. Rich states that methyl cellulose is not conventionally known to advantageously increase viscosity of proliferating cells in culture media; but rather, is used in immobilizing medium so that when cells are stimulated to proliferate and divide, they remain in place and form colonies.

Examiner concedes with Dr. Rich's statement that methylcellulose is used in culture media for immobilization purposes so that cells, when stimulated to proliferate and divide, remain in place to form colonies.

B) Dr. Rich states that transferrin is not present in the medium as described by Moore but is added as a mixture of BITSI. According to Dr. Rich, the iron saturated human transferrin of the claimed invention is used at a final concentration of 1×10^{-10} as opposed or in comparison to 5.0 mg/L as used by Moore.

In response, the claims do not appear to recite a concentration requirement for transferrin. Accordingly, it does not exclude the concentration of 5.0 mg/L as taught by Moore. Additionally, Applicant's disclosure of transferrin as added in a mixture of BITSI does not appear to encompass that which is recited in the claims. Applicant's

disclosure of BITSI provides its use in "serum free conditions" wherein the fetal bovine serum (FBS) is replaced by bovine serum albumin (BSA) in combination specifically with transferrin and insulin. Accordingly, Dr. Rich's statement with regards to use of transferrin as part of BITSI, is not commensurate in scope with the recited claims.

7. For reasons aforementioned, no claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
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August 6, 2006

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